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10/518,915	12/23/2004	Kiichiro Yano	053466-0391	7057

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,915	YANO ET AL.	
	Examiner	Art Unit	
	Amy L. Clark	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,6,8-13 and 15-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,6,8-13 and 15-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Any rejection found in the previous Office Action and not repeated herein has been withdrawn based upon Applicants' amendments to the claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 4, 6, 8-13 and 15-25 are currently being examined on the merits.

Claim Rejections - 35 USC § 112

Claims 4, 6, 8-13 and 15-25 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting or treating photoaging in a subject does not reasonably provide enablement for a method of inhibiting angiogenesis, nor does the specification provide enablement for a method of inhibiting angiogenesis, wherein the inhibition of angiogenesis inhibits wrinkles caused by photoaging of the skin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims (please note that the rejection is the same, but that the rejection has been modified to clarify the enablement rejection).

Enablement is considered in view of the *Wands* factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims,

guidance of the specification, the existence of working examples, state of the art predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: The claims are drawn to a method of inhibiting angiogenesis and a method of inhibiting angiogenesis in a subject in need thereof, wherein the method of inhibiting angiogenesis inhibits wrinkles caused by photoaging of the skin of said subject.

Breadth of the Claims: The claims are broad in that the claims are drawn to a method of inhibiting angiogenesis in a subject in need thereof, and a method of inhibiting angiogenesis in a subject in need thereof, wherein the method of inhibiting angiogenesis inhibits wrinkles caused by photoaging of the skin of said subject. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the Specification and Existence of Working Examples: The specification describes two *in vitro* experiments comprising undisclosed types of extracts of da zao (*Zizyphusjujuba* Miller var. inermis Rehder), roman chamomile (*Anthemis nobilis* Linne) , coicis semen (*Coix lacryma-jobi* Linne var. ma-yuen Stapf), and silk (*Bombyx mori* Linnaeus). The first Experiment involves a luciferase assay for screening TSP-1 inducers and Experiment 2 involves the screening of an apotosis inducer. Applicants provide two Figures that allegedly show activity of each extract studied. However, the data is confusing in that it is not clear what Applicants are measuring, particularly with regards to Experiment

2, where the results appear to be the same as the TSP-1 itself. The description of both experiments is lacking details, like how the TSP-1 activity was measured in the luciferase assay, nor is there a control using a known TSP-1 inducer to demonstrate activity. Furthermore, Applicants do not provide any indication of how they have made each extract or what the extracts are. Finally, there are no experiments conducted to demonstrate a correlation between TSP-1 activity or luciferase and inhibition of wrinkles caused by any mechanism, particularly photoaging.

The specification envisions that by administering a composition comprising at least one active ingredient selected from a group of crude drugs consisting of da zao (*Zizyphusjujuba* Miller var. inermis Rehder) extract, roman chamomile *(Anthemis nobilis* Linne) extract coicis semen *(Coix lacryma-jobi* Linne var. ma-yuen Stapf) extract, and silk *(Bombyx mori* Linnaeus) extract that the composition will inhibit angiogenesis in a subject in need thereof and that inhibiting angiogenesis inhibits wrinkles caused by photoaging of the skin of said subject.

However, no working examples are provided with regard to a method of inhibiting angiogenesis in a subject in need thereof by topical application to a subject or inhibiting wrinkles caused by photoaging of the skin of said subject.

Applicants have not provided adequate studies to demonstrate that these ingredients, either on their own or in combination, have the claimed functional effects.

Predictability and State of the Art: The state of the art at the time the invention was made was unpredictable and underdeveloped.

Filleur et al. (X1*, "In vivo mechanisms by which tumors producing thrombospondin 1 bypass its inhibitory effects". Genes Dev. 2001 June 1; 15(11): 1373–1382) teaches a method of using TSP-1 in an *in vitro* and *in vivo* study to demonstrate its effect on angiogenesis. Filleur further teaches using TSP-1 in a cell culture involving luciferase, but demonstrate that assays involving luciferase do not already contain TSP-1.

In Applicants' specification, it appears that Applicants are stating that by employing da zao (*Zizyphusjujuba* Miller var. inermis Rehder) extract, roman chamomile *(Anthemis nobilis* Linne) extract coicis semen *(Coix lacryma-jobi* Linne var. ma-yuen Stapf) extract, and silk *(Bombyx mori* Linnaeus) extract in an in vitro assay that these extracts induce TSP-1 and increase its function.. However, the assay employed does not contain TSP-1, and if it does, it is not adequately described, so it is unclear as to how Applicants arrive at the assumption that these extracts have this effect.

Thus, while the claim-designated method may be useful for providing such an effect, Applicant does not disclose a method of inhibiting angiogenesis in a subject in need thereof, or a method of inhibiting angiogenesis in a subject in need thereof, wherein the method of inhibiting angiogenesis inhibits wrinkles caused by photoaging of the skin of said subject.

Amount of Experimentation Necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could

not rely on the prior art or instant specification to teach how to use a composition comprising at least one active ingredient selected from a group of crude drugs consisting of da zao (*Zizyphusjujuba* Miller var. inermis Rehder) extract, roman chamomile *(Anthemis nobilis* Linne) extract coicis semen *(Coix lacryma-jobi* Linne var. ma-yuen Stapf) extract, and silk *(Bombyx mori* Linnaeus) extract for inhibiting angiogenesis and inhibiting wrinkles caused by photoaging.. In order to carry out the claimed invention, one of ordinary skill in the art would have to a composition comprising at least one active ingredient selected from a group of crude drugs consisting of da zao (*Zizyphusjujuba* Miller var. inermis Rehder) extract, roman chamomile *(Anthemis nobilis* Linne) extract coicis semen *(Coix lacryma-jobi* Linne var. ma-yuen Stapf) extract, and silk *(Bombyx mori* Linnaeus) extract that can be administered in a therapeutically effective dose with an acceptable level of side-effects.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 4, 6, 8-13 and 15-25 are not considered to be fully enabled by the instant specification.

Please note that the rejections below are based upon what Applicants are enabled for.

Claim Rejections - 35 USC § 102

Claims 4 and 12 remain rejected under 35 U.S.C. 102(b) as being anticipated by Uehara et al. (N1*, JP 2000-119156).

Uehara teaches a method of decreasing pigmentation in a guinea pig brought wherein the pigmentation is induced by irradiation of guinea pig skin with UV-B light comprising administering a composition comprising an extract of coix seed (*Coix lacryma-jobi*) (See paragraphs 0039 and 0040), which reads on treating photoaging in a subject in need thereof because the composition clearly treats symptoms of photoaging when applied to the skin of a subject. Uehara further teaches a method of preventing skin dullness and pigmentation comprising administering a composition comprising coix-seed extract in an amount of 0.01% or a composition comprising chamomile extract (See the Examples).

Claims 4, 11, 12 and 18 remain rejected under 35 U.S.C. 102(b) as being anticipated by Garlen et al. (B*, 4,707,354).

Garlen teaches a method for treating skin comprising covering said skin with a layer of a sunscreen, protectant, moisturizing, dermatological composition consisting essentially of a formulation comprising less than 1 wt % silk powder (See claim 8). Garlen further teaches that the method for administration of such compositions to human skin to provide rehydration and nearly complete screening of cancer-causing actinic radiation (See abstract) and protects mature

skin from cell damage and dehydration due to exposure to sunlight (See "Field of the Invention"), which reads on protecting skin against photoaging/inhibiting photoaging and treating photoaging.

Therefore, the reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

Claims 4, 6, 8-13 and 15-25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sei et al. (S*, JP 2002-128651 A), in view of Andre-Jean et al. (T*, JP 07-145067 A).

Sei teaches a photoaging inhibitor (See abstract) that has an anti-aging effect and demonstrates a high improvement effect to wrinkles (See paragraph 0077) in the form of a topical composition for administration to the skin comprising ginseng extract in an amount of 0.00001 - 10 mass %, or 0.0001 to 5% (See paragraph 0008), coix seed extract, a seaweed extract (See paragraph 0037), chamomile extract (See paragraph 0012) in an amount of 0.0001 to 3% (See paragraph 0018), silk protein (which is a type of silk extract) and a zizyphi fructus extract (See paragraph 0039). Sei further teaches that the skin care composition is administered, topically, to a mouse and that the skin care composition is administered, *in vitro*, to human skin cells (See Examples paragraphs 0041-0063).

Andre-Jean teaches a cosmetic composition for treating skin comprising 0.1-15 wt.% hydroglycol extract of alga such as Chlorella (See abstract). Andre-

Jean further teaches that the therapeutic method by these cosmetics protects the skin and hair from the exteriors, such as an oxidizer, sunrays, and a staining agent, against the element which does adverse action, maintains the organization of the skin or hair, and aims at improving the quality of the skin (See paragraph 0038), which reads on inhibiting photoaging. Andre-Jean further teaches examples of administering the cosmetic composition to the skin (See Example 1 beginning with paragraph 0040).

The method of using the referenced composition is not expressly taught as a method of inhibiting wrinkles caused by photoaging. However, the instantly claimed process is a **one-step process** of applying to skin a composition comprising .1-15 wt.% hydroglycol extract of alga such as Chlorella. Thus, the functional effect of protecting keratinous fiber from extrinsic damage is intrinsic to the method of using the composition taught by Andre-Jean particularly since the amount of an extract of chlorella administered to the skin falls within the range claimed by Applicant.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Sei by administering a composition comprising da zhao extract, ginseng extract, chamomile extract, chlorella extract, coicis semen extract, and silk extract, which are all ingredients that have the same functional effect of inhibiting photoaging. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the instantly claimed ingredients of da zhao extract, ginseng extract, chamomile extract, chlorella extract, coicis semen

extract, and silk extract for their known benefit of inhibiting photoaging and inhibiting wrinkles caused by photoaging since each claimed ingredient is well known in the art for the same purpose, as useful for weight loss and for the following reason:

It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980); *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992). As the court explained in Crockett, the idea of combining them flows logically from their having been individually taught in prior art. Therefore, since each of the references teach that da zhao extract, ginseng extract, chamomile extract, chlorella extract, coicis semen extract, and silk extract, are useful for inhibiting photoaging, it would have been obvious to combine these ingredients with the expectation that such a combination would be effective for inhibiting photoaging. Thus, combining them flows logically from their having been individually taught in prior art.

From the teachings of the references, it is apparent that one of ordinary skill in the art one would have been motivated to combine da zhao extract, ginseng extract, chamomile extract, chlorella extract, coicis semen extract, and silk extract to provide a beneficial composition for the expected benefit of inhibiting photoaging because at the time the invention was made, the instantly

claimed ingredients da zhao extract, ginseng extract, chamomile extract, chlorella extract, coicis semen extract, and silk extract were known to be useful for inhibiting photoaging, and since the ingredients and mode of administering the ingredients, which are one and the same as those claimed by Applicants, was known in the art at the time the invention was made. Thus the combined composition of da zhao extract, ginseng extract, chamomile extract, chlorella extract, coicis semen extract, and silk extract would have been expected to be even more effective for inhibiting photoaging because the claimed ingredients were all useful for this purpose, as clearly taught by the above references.

Finally, one of ordinary skill in the art would have had a reasonable expectation of success to combine the following ingredients for inhibiting photoaging to gain the benefits of individual components as part of a composition for inhibiting photoaging: da zhao extract, ginseng extract, chamomile extract, chlorella extract, coicis semen extract, and silk extract, to provide a beneficial composition for the expected benefit of inhibiting photoaging and inhibiting wrinkles caused by photoaging because at the time the invention was made, these ingredients were well known to inhibit photoaging.

Moreover, it would have been obvious to one of ordinary skill in the art, one would have been motivated and one would have had a reasonable expectation of success at the time the invention was made to modify the referenced composition because it would have been well in the purview of one of ordinary skill in the art practicing the invention to pick and choose a concentration of da zhao extract, ginseng extract, chamomile extract, chlorella extract, coicis

semen extract, and silk extract because at the time the invention was made, da zhao extract, ginseng extract, chamomile extract, chlorella extract, coicis semen extract, and silk extract were known to be useful for promoting inhibiting photoaging and the references provided herein teach amounts of the ingredients claimed. Therefore, adjusting the amount of da zhao extract, ginseng extract, chamomile extract, chlorella extract, coicis semen extract, and silk extract would have been obvious to enhance the effect of these ingredients. Thus, the claimed invention is no more than the routine optimization of a result effect variable.

Based upon the beneficial teachings of the cited references, the skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with regards to the rejection under 35 USC 112, 1st paragraph have been carefully considered, but are not deemed to be persuasive of error in the rejection.

Applicants argue that the specification discloses that luciferase activity was measured with Promega Luciferase Assay System, which is well known in the field. Applicants further argue that in Experiment 2, the object is to screen

agents capable of exhibiting TSP-1 function and that cell death was detected by Apoptag Plus Fluorescein In Situ Apoptosis detection kit and that the experiments are detailed and readily available to the public. Applicants further argue that main components of the extracts are described in the specification and the extracts are commercially available. Applicant further argues that a method of inhibiting angiogenesis is well supported and enabled in view of the references submitted by Applicants and that reagents that inhibit angiogenesis can effectively prevent or inhibit aging.

However, this is not found persuasive because while it is appreciated that the extracts are disclosed on pages 6 and 7, the type of extract used is not illuminated. Merely disclosing a few components and what it is known to be useful for are not adequate descriptors. The idea behind disclosing how the extracts were made and what the extracts are is so that one of ordinary skill in the art would be able to know what product is being used in order to fully understand the invention. Since the ingredients are ambiguous at best and not clearly disclosed or defined, it would not be clear to one of ordinary skill in the art what ingredients are being used in Applicants' instantly claimed invention. With regards to the instrumentation and the experimental section, while it is appreciated that such equipment has the functions disclosed by Applicants the issue is more with regards to whether Applicants are enabled for the method as claimed. In the art, there is no clear nexus between TSP-1 and angiogenesis in humans, which is where Applicants' are intending this method be employed. Since the art does not support a correlation, particularly in vivo in humans,

between the in vitro experiment and what is being claimed, Applicants are not enabled for what Applicants are claiming. As far as enablement for inhibiting aging, Applicants are not enabled for inhibiting aging. There is no evidence that aging can be inhibited, which is why people age and why skin ages and is constantly aging. While the process can be accelerated by smoking, uv exposure and dehydration, there is no evidence to show that the process for skin aging, particularly in vivo, can be inhibited or prevented. This same principle applies to wrinkle formation. All skin is prone to develop wrinkles and there is no way to prevent wrinkles from forming. Further, Applicants' experiments with regards to TSP-1 appear to be for screening for an apoptosis inducer, which is in no way related to inhibiting wrinkles and aging.

Applicants' arguments with regards to the rejection under 35 U.S.C. 102(b) and 103(a) have been carefully considered but are not deemed to be persuasive of error in the rejection.

Applicants argue that claims 4, 12 and 19 recite "a method of inhibiting angiogenesis in a subject in need thereof...", that Uehara teaches a whitening agent comprising coix seed, Garlen teaches a cosmetic product containing silk powder as merely an auxiliary component, Sei teaches using roman chamomile as an anti-inflammatory ingredient and coicis semen as a whitening agent andAndre- Jean teaches a cosmetic composition containing Chlorella as an anti-inflammation reagent. However, all of the prior art references are completely silent regarding activities of the crude drugs for inhibiting angiogenesis.

This is not found persuasive because Applicants are not enabled for "a method of inhibiting angiogenesis in a subject in need thereof...". Furthermore, the ingredients taught in the 102(b) and 103(a) references are present in the amounts claimed by Applicants and are administered in the same way as claimed by Applicants. With regards to the Sei reference, Sei teaches that the instantly claimed ingredient of silk extract is an active ingredient in the composition. Further, Applicants use open claim language which does not prevent other active ingredients to be present in a composition comprising Applicants' instantly claimed ingredients. Sei expressly teaches "silk protein" in paragraph 0039, which is a type of silk extract, and "zizyphi fructus extract", also in paragraph 0039, which is synonymous with da zao. Applicants are invited to further define their invention by closing the claim language and by further describing the type of extract Applicants' are employing (for example: aqueous, ethanol, hexane, organic, etc.) used in the method, provided they have appropriate support in the specification.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy L. Clark whose telephone number is (571)272-1310. The examiner can normally be reached on Monday to Friday between 8:30am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571) 272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amy L Clark/
Primary Examiner, Art Unit 1655